

# The role of IL-23 in the immunopathogenesis of psoriasis

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## Abstract

In just 10 years from its discovery in 2000, interleukin-23 has quickly moved from being recognized as a pro-inflammatory cytokine to a key player and potential therapeutic target in psoriasis.

## Introduction and context

Interleukin-23 (IL-23) is a heterodimeric cytokine, consisting of a unique IL-23p19 subunit paired with a common IL-12/23p40 subunit, which is shared with IL-12 [1]. It is mainly produced by activated myeloid cells, as well as epithelial and endothelial cells, and signals through its heterodimeric IL-23 receptor complex, consisting of a unique IL-23 receptor (IL-23R) subunit paired with a common IL-12Rβ1 subunit shared with the IL-12 receptor complex (Figure 1) [2]. Shortly after its discovery, IL-23 emerged as a key pro-inflammatory cytokine driving autoimmunity, in both animal models and human diseases. In mice, lack of IL-23 was found to make them resistant to animal models of arthritis and multiple sclerosis [3,4]. In addition, models of experimental colitis pointed towards a role for IL-23 as a key tissue-specific effector cytokine that amplifies the inflammatory response [5,6]. In humans, IL-23 was found to be over-expressed in clinical samples of several immune-mediated diseases, including Crohn's disease, rheumatoid arthritis and multiple sclerosis. At the same time, IL-23 was strongly implicated in the development of a novel, IL-17A-producing T helper (Th)17 cell subset, which had just been discovered and identified as a main player in autoimmunity [7].

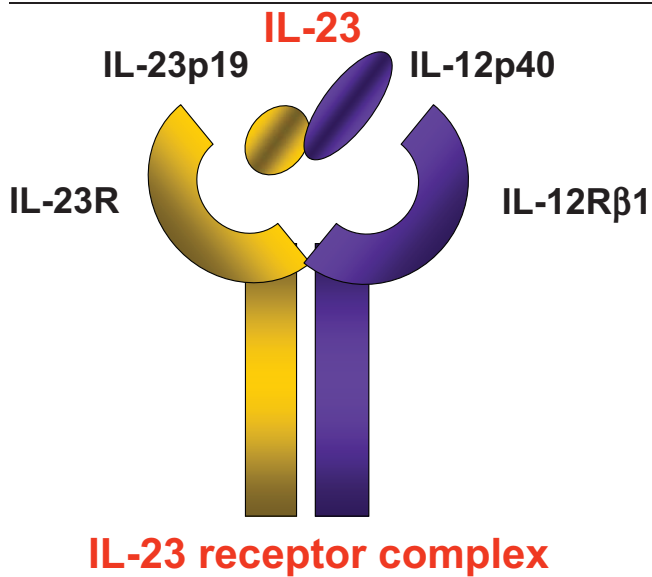
These findings have set the scene for a major re-evaluation of the immunopathogenesis of psoriasis. Psoriasis is a T-cell-mediated, chronic inflammatory skin disease that results from a complex interplay between environmental and genetic factors [8]. Psoriasis had been traditionally regarded as a Th1-type and tumor

necrosis factor (TNF)-driven disease but this perception was challenged after the discovery of IL-23 and experimental and clinical data that put the spotlight on the IL-23/Th17 axis in psoriasis.

Intradermal injection of IL-23 or over-expression of IL-12/23p40 in mouse keratinocytes (KCs) was shown to lead to erythema, induration and prominent dermal papillary blood vessels with histopathological features resembling psoriasis [9,10]. IL-23 was found to be highly expressed in psoriatic skin lesions, where it is mainly produced by tissue-resident and/or recruited dendritic cells (DCs) with some possible contribution by KCs [11,12]. Moreover, the clinical benefit from conventional and biologic systemic therapies targeting psoriasis was found to correlate with IL-23 down-regulation in psoriatic patients [13,14], and a proof-of-concept phase I study testing efficacy and safety of ustekinumab, a human monoclonal antibody directed against IL12/23p40, showed promising results in the treatment of moderate to severe psoriasis [15]. Consistently, IL-17A was shown to be expressed in psoriatic skin [9], suggesting that Th17 cells could possibly infiltrate psoriatic lesions, contributing to chronic inflammation.

## Major recent advances

In the past 3 years major advances in our understanding of psoriasis pathogenesis have arisen from exciting genetic, immunological and clinical findings, all unambiguously converging on the pivotal role of the IL-23/Th17 axis in psoriasis [16].

**Figure 1. Interleukin-23 and its receptor complex**

Interleukin (IL)-23 is a heterodimeric cytokine composed of IL-12/23p40 and IL-23p19 subunits. It binds to the IL-23 receptor complex composed of IL-12R $\beta$ 1 and IL-23R subunits.

Genome-wide association studies have clearly and repeatedly shown that several genes of the IL-23 pathway are associated with psoriasis. We and others have found that single nucleotide polymorphisms in both the *IL12B* and *IL23R* genes, coding for IL-12/23p40 and IL23R subunits, respectively, are associated with psoriasis [17,18]. Of interest, the non-synonymous nucleotide substitution in the *IL23R* gene, resulting in an arginine to glutamine exchange (Arg381Gln) in the cytoplasmic domain of the receptor, has a protective role not only in psoriasis, but also in other immune-mediated diseases, including Crohn's disease [19], suggesting that genetic variants in the *IL23R* gene might be common determinants of autoimmunity. Finally, a genetic association with psoriasis has recently been found also for variants in the *IL23A* gene, which codes for the IL-23p19 subunit [20].

Human Th17 cells have been thoroughly characterized with respect to their cytokine requirements (transforming growth factor-beta plus one of several pro-inflammatory cytokines, i.e., IL-6, IL-1 $\beta$ , IL-23 and IL-21), lineage markers (master regulator transcription factor ROR $\gamma$ t and surface markers CCR6 and IL-23R) and cytokine production (IL-17A, but also IL-17F, IFN- $\gamma$ , IL-22 and IL-26) [21,22]. Likewise, the role of IL-23 with regard to Th17 cell biology has been clarified and refined. Although not required for early Th17 development, IL-23 plays a role in terminal differentiation of

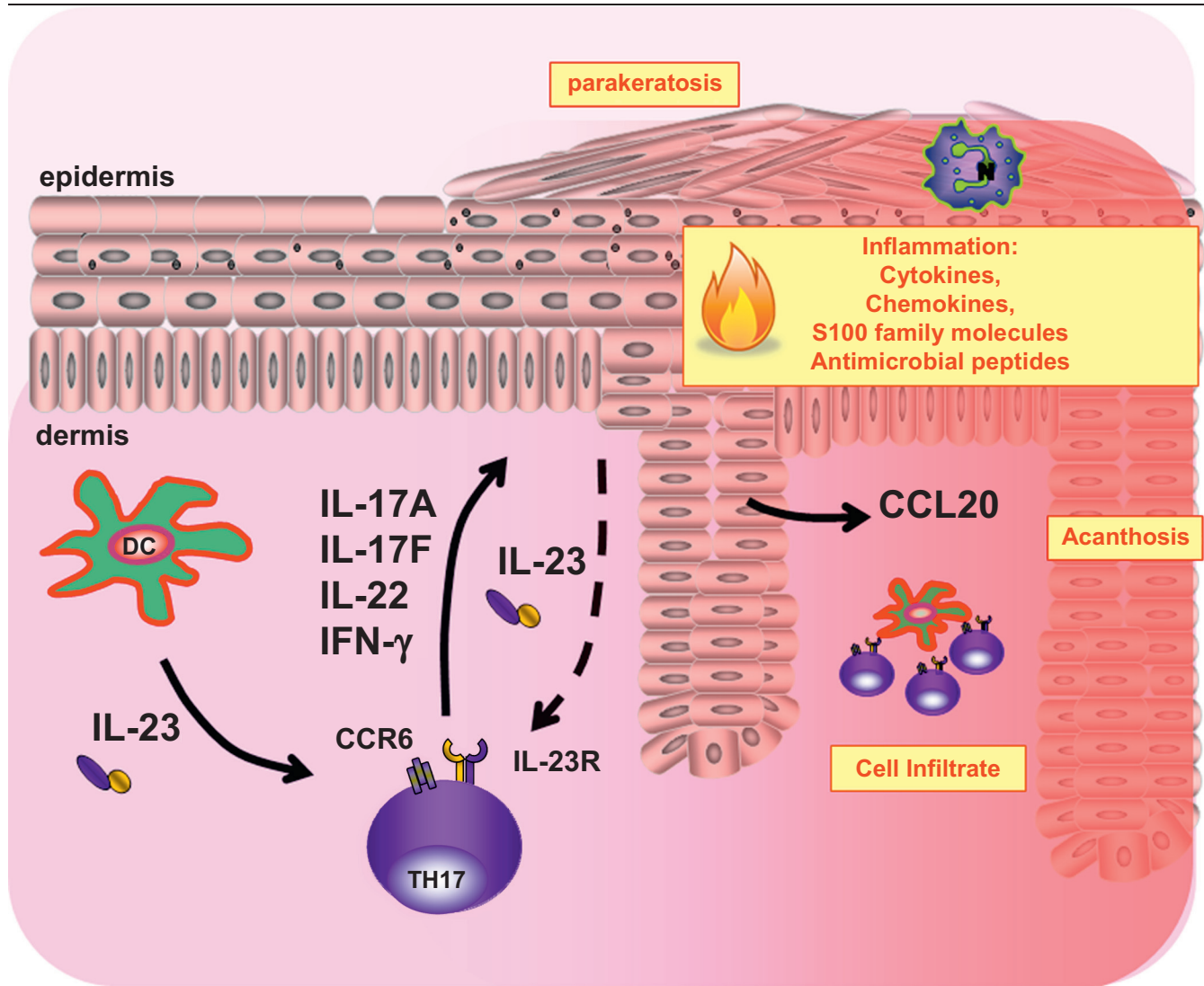
effector Th17 cells and their pathogenicity in peripheral tissues [23]. These findings are of relevance to psoriasis as Th17 cells have been identified in psoriatic skin [24] and Th17 cytokines have been found to be expressed at high levels in lesional skin and to induce the production of antimicrobial peptides and chemokines by KCs [21]. Of particular interest is the link between IL-23 and IL-22 production by Th17 cells. IL-23 injection in mice induces IL-22-dependent dermal inflammation, KC hyperproliferation and epidermal acanthosis [25], while IL-22 neutralization is able to prevent the development of psoriasis-like skin lesions [26]. Moreover, CCR6 also seems to be required for IL-23-induced and IL-22-mediated psoriasis-like skin inflammation in mice [27], and it has been shown that Th17 cytokines can stimulate the production of the CCR6 ligand CCL20 by KCs, suggesting a possible mechanism by which Th17 cells maintain their continual presence in psoriatic skin [28]. Therefore, in the 'IL-23/Th17 axis' model of psoriasis, IL-23 secreted by dermal DCs is able to induce Th17 cell activation and the release of pro-inflammatory Th17 cytokines that acts on KCs, which, in turn, sustain and amplify the chronic inflammatory disease process by producing more IL-23 as well as pro-inflammatory cytokines, chemokines, members of the S100 family and antimicrobial peptides (e.g., TNF, IL-8, CCL-20, S100 molecules, defensins and cathelicidins; Figure 2).

The anti-IL-12/IL-23 monoclonal antibody ustekinumab has been approved in Canada (December 2008), Europe (January 2009) and USA (September 2009) for human use in moderate to severe psoriasis. Designed in the late 1990s with the aim of blocking IL-12 (IL-23 was still unknown at that time), ustekinumab targets the common IL-12/23p40 subunit, thus blocking both IL-12 and IL-23 signalling. Phase 3 clinical trials (Phoenix 1 and Phoenix 2) involving more than 2000 patients have shown that up to 76% of patients achieve at least a 75% improvement in the Psoriasis Area and Severity Index (PASI 75) at week 24, with only mild and non-serious adverse events [29,30]. Very recently, ustekinumab has shown higher efficacy than the anti-TNF drug etanercept, with 71% of patients in the high-dose ustekinumab group achieving PASI 75 compared to 49% in the etanercept group after 12 weeks. Interestingly, up to 49% of the non-responders in the etanercept group had a PASI 75 response when crossed over to high-dose ustekinumab [31].

### Future directions

IL-23 represents one of the rare instances in which basic science has rapidly progressed to preclinical studies and resulted in a clinical intervention that supports the

Figure 2. The interleukin (IL)-23/Th17 axis in the immunopathogenesis of psoriasis



In the 'IL-23/Th17 axis' model of psoriasis, T helper 17 (Th17) cells interact with skin-resident cells, contributing to the psoriatic disease phenotype, characterized by scaly plaques and thickened epidermis (acanthosis), with elongated rete ridges and hyperproliferative keratinocytes (KCs) retaining the nucleus in the stratum corneum (parakeratosis), as well as dermal inflammatory cell infiltrate. IL-23 secreted by dermal dendritic cells (DCs) is able to induce Th17 cell activation with production of pro-inflammatory cytokines such as IL-17A, IL-17F, IL-22 and IFN- $\gamma$ . These cytokines act on KCs, inducing epidermal hyperplasia and KC activation. Activated KCs produce pro-inflammatory mediators, including chemokines, members of the S100 family, pro-inflammatory cytokines and antimicrobial peptides. In particular, CCL20 is able to recruit more CCR6+ Th17 cells. Moreover, KCs might produce IL-23, which could mediate crosstalk with Th17 cells in synergy with IL-23 produced by dermal DCs, thus further sustaining and amplifying skin inflammation.

efficacy of IL-23/IL-12 targeting in the treatment of psoriasis. However, several questions remain to be answered. First, what is the functional role of the IL-23 pathway gene variants associated with psoriasis? Second, is there any correlation between these genetic variants and disease phenotype? Third, are the newly discovered genetic variants of any use in pharmacogenetic studies to predict treatment response?

Moreover, a recently described Th cell subset, IL-22-producing Th22 cells, has been identified in psoriasis [32]. It will be interesting to investigate if IL-23 plays a role in Th22 activation in psoriasis. Finally, the ultimate question is whether inhibition of IL-23 on its own, with either monoclonal antibodies or small molecules, is effective. Clinical studies to test the safety and effectiveness of a monoclonal anti IL-23 are currently under way

and will provide us with useful new insights into the role of IL-23 in the immunopathogenesis of psoriasis.

### Abbreviations

DC, dendritic cell; IL, interleukin; IL-23R, IL-23 receptor; KC, keratinocyte; PASI, Psoriasis Area and Severity Index; Th, T helper; TNF, tumor necrosis factor.

### Competing interests

FON has provided consultant advice to Centocor Inc. (Horsham, PA, USA), Abbott Laboratories (Abbot Park, IL, USA) and Janssen Cilag (High Wycombe, Buckinghamshire, UK). PDM declares that she has no competing interests.

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